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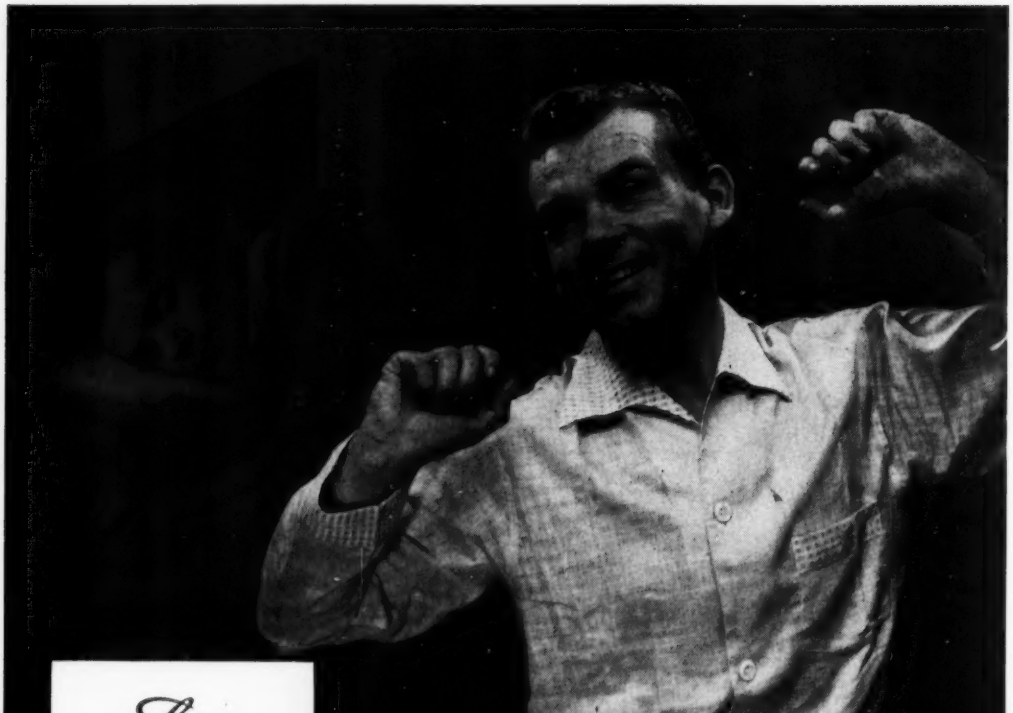

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Southwestern MEDICINE

VOL. XXXVIII APRIL, 1957 No. 4

EDITORIAL

Medical Education Week

The impressive story of the accomplishments of U. S. medical schools will be told to the nation during the second annual observance of Medical Education Week, April 21-27, and the Southwestern Medical Association has been invited by the national sponsors to develop plans for community programs in this area.

The purpose of the observance is to focus the attention of the American people on the national importance and indispensability of medical education. A well-organized program of public information will bring about greater friendship and support for the medical schools by creating a better understanding of their aims, problems, achievements, and public services.

Eisenhower Endorsement

President Eisenhower, in his personal endorsement of this observance, said, "While the benefits of health and medical education are daily with us, it is fitting to devote a special week to the consideration of the wider training of physicians. Each American has a personal stake in our country's medical schools. The schools which train the physicians required by our growing population are a vital resource for the health of our people and the strength of the Nation."

Specific aims of Medical Education Week, if pursued effectively, will demand the participation of a large portion of our members. These are the goals:

1. To portray the key role that medical education plays in the promotion and maintenance of the nation's health and security, and make the public aware that the nation's 82 medical schools are the foundation of our entire health and medical structure.

High Standards

2. To explain how the medical schools are striving to meet the demand for larger numbers of physicians and, at the same time, to maintain the high standards of training that have come to characterize American medical education.

3. To call attention to the steady progress in the medical sciences, showing what this means in terms of longer life, better health and greater freedom from disease and disability.

4. To point out the wide range of activities — teaching, research, service and leadership — carried on by the modern medical school in addition to its job of training new doctors.

5. To make clear the extent and nature of the new challenges to the profession, some growing out of our constantly expanding fund of medical knowledge and some resulting from the mounting complexity of our civilization.

6. To point out some of the steps being taken constantly to push back the horizons of the medical sciences and to realize the full potential of the nation's health resources.

National Sponsors

While medical societies and medical schools throughout the country build community programs around these objectives, the national sponsors — the AMA and the Woman's Auxiliary, the Association of American Medical Colleges, the Student AMA, the American Medical Education Foundation, and the National Fund for Medical Education — are enlisting the help of newspaper syndicates, radio and television networks, popular and professional publications, civic groups, industry, and commerce in a broad program of national publicity and promotion.

In view of this fertile opportunity to further the goals of medical education, all physicians are urged to demonstrate their gratitude to their alma maters by working actively with their planning groups to help all 82 medical schools win the friendship and support of the public during this Medical Education Week, April 21-27.

CURRENT THERAPY

Treatment of Rheumatic Fever*

By Jack A. Bernard, M.D., F.A.C.P., El Paso

Penicillin should be given at once to eradicate the hemolytic streptococcal carrier state.

Prophylaxis should then be begun and continued indefinitely to prevent further infection with hemolytic streptococci.

If there is no evidence of carditis, salicylate alone probably is preferable to hormone therapy. Recommended dosage is one grain per pound of body weight daily for two days (up to a maximum of 10 grams), then two-thirds grain per pound daily for five days and then one-half grain per pound daily for three weeks. After this, salicylate can be reduced one gram daily, provided the C-reactive protein has disappeared from the blood and does not return, save for a possible transient "rebound" after salicylate has been discontinued.

Smoldering Carditis

If C-reactive protein has not disappeared by the end of four weeks it is highly probable that the patient has smoldering carditis, and cortisone probably is indicated. Giving the salicylate in divided doses of one gram (15 grains) each appropriately spaced through the day is less apt to lead to acute salicylate toxicity than are larger doses given at wider intervals.

In the presence of carditis it has been recommended that cortisone be started *at once* in doses of 300 mg. daily by mouth. This is continued for six weeks, after which the dose is reduced half a tablet (12.5 mg.) daily. Because of the salt-retaining size of the dosage, a rigid diet containing less than 50 mg. of sodium daily is imperative.

Potassium Chloride

To counteract the possibility of potassium depletion, potassium chloride in enteric-coated tablets is given in doses of 1.0 gm. two or three times daily after meals. While six weeks of cortisone usually suffice, further treatment is indicated if the C-reactive protein is still present.

A transient "rebound" when hormone is stopped does not call for further treatment. The C-reactive protein may return at this time but usually disappears in about two weeks. However, if a true relapse occurs or if clinical evidence or if the C-reactive protein or other laboratory evidence of continuing low grade carditis persists, cortisone should be resumed.

Dosage Outlined

If salicylate is to be given together with cortisone, the dosage may be outlined as above. However, on theoretic grounds, in the hope of minimizing the rebound phenomenon, it has been advised to continue salicylate dosage at the level of one-half grain per pound of body weight daily for three weeks after cortisone has been stopped.

The cooperative study of the value of cortisone, corticotropin and salicylates in rheumatic fever has raised anew the question whether salicylates may not, after all, exert a beneficial effect on the heart lesions. It has been found in a carefully conducted analysis of a large number of patients that those who receive salicylates fared about as well as those treated with cortisone or corticotropin.

At the same time the evidence that the hormones do exert a beneficial effect when given early in carditis has led to the obvious conjecture that perhaps salicylates too, may be of help.

*This is the third of a series of articles on Rheumatic Fever by Dr. Bernard.

New Postgraduates Courses at New York University

Two new full-time courses on the management of chronic kidney disease and of hypertension are to be given by the New York University Post-Graduate Medical School from June 24 through 27.

The management of chronic kidney disease (June 24-25), under the direction of Dr. Lawrence G. Wesson, will deal with the selection and interpretation of clinically available tests for the estimation of renal function. The advantages and disadvantages of each test will be considered.

The management of hypertension (June 26-27), under the direction of Dr. J. Marion Bryant, will be concerned with the presentation, with appropriate clinical demonstrations, of the following subjects: a brief summary of etiologic theories, psychological factors, the natural course, relative significance of blood pressure levels, eye grounds, cardiac silhouette, electrocardiogram, renal function, significance of obesity and arteriosclerosis, and unilateral renal disease. Emphasis is placed upon the use of hypotensive drugs. Other therapeutic measures, such as sympathectomy, nephrectomy, and diet-therapy are reviewed.

THE PRESIDENT'S COLUMN

Longer Lives for Doctors

By Celso C. Stapp, M. D., El Paso

Statistically speaking, each and every doctor should live beyond the sixtieth year. That would be assuming that the American doctor is a male individual and many other ifs, ands and buts. Narrowing it down to a professional group, one might ask, is the physician as a professional group committing a special type of genocide?

Recently a very good friend of mine, who is an internist, had a coronary and came precariously close to dying in said initial attack. When one who is older than you has a coronary, you may shrug your shoulders and pass it off as just that he is getting old. As you become older and pass through some of the years in which some of your erstwhile colleagues have had coronaries and have died, the inventory starts.

This is more emphasized when one younger than you has one. The fact that he is on the road to recovery is very little consolation to you. He may have followed the latest theories on how not to have a coronary or may have worked a very carefully planned schedule, primarily based on a theory that it will still prevent physical collapse.

Inventory

An inventory is then made of those who are considered by yourself as the oldsters, and you see that their living may not have been self-planned as those who have gone on. Can we plan ourselves out of falling by the wayside? We know that we cannot choose our ancestors and thus help out in the plan of living to a ripe, "useful," old age. Is it hard work that is killing the profession? The dictum "hard work never killed anyone, but worry has put many a good man in the grave" may hold true in our profession.

We, as doctors, dispense volumes of advice on how to live long and be happy, and I am sure to some extent we try to follow part or all of this direction. We even tell people not to worry, but can we give them the plan and can we follow it ourselves?

Although medical science has done much to eliminate organic disease we have not done so well in helping ourselves and our patients out of the stress diseases which have become a part of our very complicated civilization.

Volumes of Advice

Adding to the volumes of advice may I add a bit that my grandfather once said and which I still feel holds true. "It is not what goes into your stomachs that will kill you but what goes on in your head. Keep a clean conscience and tend to your own knitting. Love your neighbor and help him and he will help you.

"Money is no good when you are dead but God and your friends are as they can go on with you forever!"

Maybe I will be next, maybe you, only time will tell. Statistically we will live a long time. I do not think that we fear death. What most of us fear is being an invalid.

I think that what my grandfather advised holds true in some degree in keeping us out of this plight.

Patient-Doctor Relationship

"The Changing Patient-Doctor Relationship" by Martin G. Vorhaus, M. D. will be published by Horizon Press, New York, on March 18th. This book explores, for the layman what has come to be recognized as a necessary part of medical treatment — the need of both patient and doctor to arrive at a healthier understanding of each other. Clearly written in non-technical terms, it is the result of more than thirty-five years of experience in treating men and women of every age.

The major part of the book is devoted to five long, detailed case histories: two of women and three of men. Presented in a new way, through revealing conversations over long periods of time between patient and doctor, each case becomes an intimate life history. Through it, the reader witnesses, within the privacy of the doctor's office, the treatment of the human being in deepest distress; from secret worry over illness to hesitant and then frank expression, from troubled withdrawal to renewed effort, often from relapse to encouragement skillfully inspired; ultimately from exciting awareness to a positive measure of health.

Edited by Andrew M. Babey, M. D., Las Cruces, N. M.

APHORISMS and MEMORABILIA

Miscellaneous Truths and Concepts

1. "Sympathectomy for hypertension shares with laminectomy for prolapsed disc and vagotomy for peptic ulcer the questionable distinction of having been among the most fashionable operations of recent years. Yet, it has lately been said that "few operations" are more dead today. . . . . But the fact that sympathectomy does not cure hypertension does not mean that it cannot help many hypertensive patients." Leading Articles, *The Lancet*, Nov. 17, 1956, Page 1031.

2. "Prostate glands removed at necropsy from patients who have died of some other disease are commonly found to contain histological carcinomas. This remarkable finding was reported by Rich in 1935 and has since been confirmed by very many workers. At least 30 per cent of all men over 50 years old have these lesions. These tumors are indistinguishable histologically from active clinical cancers, yet they have not grown and killed the patient." Special Articles, *The Lancet*, Nov. 17, 1956.

3. "A person who exhibits symptoms of hypoglycemia on one occasion at a level of 30 mg. per cent may on other occasions have a blood sugar as low as 20 mg. per cent and yet be asymptomatic . . . . . It has been suggested that the rate of fall of the blood sugar level is important in determining the type of resulting symptom complex." Milton R. Porter and Virginia K. Frantz, *The American Journal of Medicine*, December 1956, Page 944.

Matter of Record

4. "It is a matter of record in most series, including our own, that whatever the nature of the symptom complex in a given individual with recurrent spontaneous hypoglycemia the attacks tend to follow the same pattern each time." *loc. cit.*, Page 945.

5. "Certain generalizations can be made about this group: the attacks are usually unrelated to fasting, rarely occur before breakfast; they often occur in relationship to periods of emotional stress; and the fasting blood sugar is not consistently low. Further, the condition is not relentlessly progressive as it is in the organic hypoglycemias. In these respects functional hypoglycemia is in direct contrast to hypoglecemia due to a tumor." *loc. cit.*, Page 947.

6. "It is an error to seize upon an obvious adenoma and hustle out of the abdomen. As has been mentioned, 18.6 per cent of these lesions in our series are multiple, and the operation will fail unless all the adenomas are found and removed." *loc. cit.*, Page 957.

7. "If I were to develop a duodenal ulcer resistant to medical treatment, such are my misgivings at present about gastrectomy that I think I would try to persuade my old chief to emerge from his retirement, to perform upon me a simple gastrojejunostomy, and to allow me to take my chance of a stomach ulcer." Eric L. Farquharson, *The Lancet*, Oct. 27, 1956, Page 851.

Overwhelming Evidence

8. "In S. B. E. due to Str. viridans the evidence overwhelmingly incriminates the teeth as the all-important source of infection. So long as teeth or fragments of teeth remain in the jaws a formidable, but preventable, hazard is ever present in the lives of these patients, and we postulate that in all patients who develop S. B. E. due to Str. viridans scrupulous complete dental clearance should be carried out as an essential item of the therapeutic attack upon the disease." F. G. Hobson, *British Medical Journal*, Dec. 29, 1956, Page 1505.

9. "Plasma and serum increase plasma volume, according to their protein content. In calculating the size of the transfusion that a patient needs, the electrolyte content of the transfusion fluid must be ignored. Thus 540 ml. citrated blood contain 430 ml. of blood and 120 ml. of citrate-dextrose solution. If a patient is calculated to have lost 2000 ml. of blood, he needs five, not four bottles of citrated blood to restore his blood volume." *Blood Transfusion in Clinical Medicine*, P. L. Mollison, Oxford, Page 63.

10. "Studies in adults have shown that after the loss of 500 ml. of blood it takes 50 days for the haemoglobin to reach its original level. After the loss of 200 ml. of blood, the average time was distinctly shorter (23 days in seven cases)." *loc. cit.*, Page 65.

(To be continued)

Free Cardiac Surgery Program

National Jewish Hospital at Denver is expanding its cardio-vascular program. It will consider applications for admission in behalf of patients suffering from cardio-vascular defects amenable to surgical intervention, including mitral and aortic stenosis, congenital cardiac anomalies, etc. Definite diagnosis is not necessary prior to admission, inasmuch as the hospital has a completely equipped cardio-pulmonary physiology laboratory for this purpose.

Patients are accepted without respect to race, religion, or national origin, and without charge. Only those unable to pay for private care are eligible. Periodic reports are made routinely to the referring physician and the patient is directed to report to him after discharge.

"POINTERS"

From the Case Records of the Massachusetts General Hospital,* 1953

(Continued)

13. "Silent mitral stenosis is rare; only three cases had been seen at the Mass. Gen. Hosp. up to 1953;" A Composite; *loc. cit.;* p. 781.

14. ". . . it is possible to remove one lung by pneumonectony so that only half the pulmonary vascular bed remains without creating pulmonary hypertension." *loc. cit.;* p. 866.

15. "Regional enteritis traditionally has four stages — a stage in which it simulates acute appendicitis, a chronic-diarrhea stage, an obstructive stage and a fistulous state." *loc. cit.;* p. 907.

16. ". . . focal convulsions in hepatic failure should always lead to the strong suspicion that there is a focal cerebral lesion in addition to any alteration of brain function associated with the cholemic state." *loc. cit.;* p. 987.

Poor Procedure

17. "Under any conditions a splenectomy is a poor therapeutic procedure for the treatment of bleeding esophageal varices, because . . . it may preclude a satisfactory portacaval shunt. Unfortunately, many surgeons are still performing splenectomies for bleeding esophageal varices." *loc. cit.;* p. 1027.

18. "When patients have resting pain with arterial insufficiency, it is an ominous sign indeed." *loc. cit.;* p. 1029.

19. "One of the important reasons for continued periodic follow-up study of diabetic patients is to provide early diagnosis and prompt, vigorous treatment of asymptomatic urinary-tract infection, which is frequent in diabetes. Pyuria in a diabetic patient should never be ignored. Catheterization should be avoided whenever possible or performed only under the most rigidly aseptic technic. In cases of obscure fever in diabetic persons the urinary tract should be thoroughly studied." *loc. cit.;* p. 1069.

20. ". . . benign gastric ulcer is a rare disease in women." *loc. cit.;* p. 76.

Clinical Judgment

21. ". . . one of the best tests of clinical judgment is to have to decide which of many symptoms and signs are relevant to the main clinical problem and which ones may be disregarded." *loc. cit.;* p. 157.

22. "Coffee-grounds vomitus is a frequent agonal symptom with all serious neurologic diseases that produce coma and will probably be explained by erosions of gastric mucosa rather than frank ulceration." *loc. cit.;* p. 159.

23. "(Arteriovenous aneurysm in the lung) . . . is one of the few radiographic appearances that is pathognomonic, and the diagnosis may be made unequivocally." *loc. cit.;* p. 162.

24. "In the presence of polycythemia a complicating tumor is not uncommon. In one reported series of patients with polycythemia the incidence of cancer was extremely high — 10 to 15 per cent." *loc. cit.;* p. 205.

*We are grateful to Dr. Benjamin Castleman, Editor of "Case Records" and Dr. Joseph Garland, Editor of "The New England Journal of Medicine" for permission to publish these excerpts. They will appear regularly and cover the years 1951 through 1955. — Andrew M. Babey, M. D.

European, Bermuda Tours Are Scheduled by A. M. A.

Post-Session tours to Europe and Bermuda are being offered A. M. A. members following the Association's Annual Session in New York, June 3-7.

Two European tours are offered — one of 24 days to France, Italy, Switzerland and Belgium, and one of 38 days, which is a longer holiday, visiting England, Belgium, Holland, Germany, Switzerland, Austria, Italy and France.

In cooperation with the World Medical Association, special scientific sessions of exceptional interest have been planned in London, Paris and Geneva.

In addittion to Europe, the post-session program includes three trips to Bermuda, designed for those who may not have sufficient time for a European vacation. One trip is five days long — the other eight days, with an opportunity to make the round trip by air, or go one way by air and one way by steamer.

Chest Physicians to Meet in New York

The 23rd Annual Meeting of the American College of Chest Physicians will be held at the Hotel Commodore, New York City, May 29 through June 2. The scientific program will include prominent speakers on all aspects of heart and lung diseases. In addition to formal presentations, there will be a number of symposia, round table luncheon discussions, seminars, and motion pictures.

The fireside conferences, which were inaugurated at the annual meeting of the College in 1955, have become more and more popular and will be repeated. At this session, more than 50 experts will be present to lead the discussions on many subjects of current interest in the specialty of diseases of the chest.

Examinations for Fellowship in the College will be held on Thursday, May 30. On Saturday evening, June 1, more than 150 physicians will receive their certificates of Fellowship at the annual Convocation, which will precede the President's Banquet.

MEETINGS

Texas Orthopaedic Association to Meet in Dallas, April 29

Plans for the annual meeting of the Texas Orthopaedic Association in Dallas, April 29, 1957, in connection with the annual meeting of the Texas Medical Association, have been announced by Dr. John J. Hinchey of San Antonio, President.

The morning program will be held in the roof garden of the Adolphus Hotel, with luncheon in the roof garden, and the afternoon program in Southwestern Medical School. Speakers and their subjects are as follows:

Dr. Charles F. Gregory of Dallas, Chairman and Associate Professor of the Division of Orthopaedic Surgery in the University of Texas Southwestern Medical School, "Poliomyelitis in Dallas, 1956, and its Relation to the Salk Vaccine."

Dr. H. R. McCarroll of St. Louis, Assistant Professor of Clinical Orthopaedic Surgery in the Washington University School of Medicine, "Management of Congenital Dysplasia and Congenital Dislocation of the Hip in Infancy."

Dr. T. O. Shindler of Houston, "Tissue Culture Compression Studies on Bone Cells."

Dr. Preston A. Wade of New York City, Professor of Clinical Surgery at Cornell University Medical College, "Importance of Joint Motion in the Treatment of Fractures."

Dr. H. H. Brindley of Temple, Texas, Scott and White Clinic, "Chamley Type Arthroplasty of the Hip."

President's Address by **Dr. John J. Hinchey of San Antonio.**

Dr. D. C. Hucherson of Houston, Clinical Associate Professor of Orthopaedic Surgery at Baylor University College of Medicine, "Arthrodesis of the Shoulder — A New Method."

Panel: "Diagnostic and Therapeutic Orthopaedic Problems" with Dr. C. F. Gregory as Moderator and Panelists Dr. H. R. McCarroll, Dr. Louis W. Breck, El Paso, Dr. Henry C. McDonald, Fort Worth, and Dr. Duncan McKeever, Houston.

Born in Battle Creek

Born in Battle Creek, Michigan, Dr. Gregory received his M. D. from Indiana University School of Medicine, and took postgraduate training in Orthopaedic Surgery in the Indiana University Medical Center, from 1948 to 1951. He was Instructor in Orthopaedic Surgery at the Indiana University School of Medicine from 1951 to 1954. He served in the U. S. Navy Medical Corps during World War II and the Korean War.

Dr. McCarroll was born in Walnut Ridge, Arkansas, and received his M. D. degree from the Washington University School of Medicine. He took his Internship and was Assistant Resident in Surgery in Barnes Hospital in St. Louis, Missouri from 1931 to 1932; he was Assistant Resident in Billings Hospital, Chicago, 1933 to 1934; and Resident in the Shriner's Hospital for Crippled Children, in St. Louis, Missouri from 1934 to 1937. He is on the staff of the Barnes Hospital, the St. Louis Children's Hospital, St. Luke's Hospital, and the Shriner's Hospital for Crippled Children in St. Louis.

Dr. H. R. McCarroll

Interned in Philadelphia

Dr. Shindler was born in Hempstead, Texas, and received his M. D. from the University of Texas Medical Branch in Galveston, Texas. He took his Internship in the Episcopal Hospital in Philadelphia, and received his Orthopaedic training in the Hermann

Dr. T. O. Shindler

Hospital (Shrine Service) in Houston and the University of Texas Medical Branch. He served in the Army Medical Corps from July, 1944, to September, 1946. In 1951, he entered private practice in Houston. He has done research in the field of compression studies and has published an article on "The Influence of the Contact Compression Factor on Osteogenesis in Surgical Fractures."

Dr. Wade was born in Helena, Montana, and received his M. D. from Cornell University. He is Attending Surgeon in New York Hospital; Chief of Combined Fracture Service in New York Hospital — Hospital for Special Surgery; and Chairman of the Committee on Trauma of the American College of Surgeons.

Born in Temple, Texas, Dr. Brindley received his M. D. from Washington University School of Medicine, in St. Louis, Missouri, and took his Internship in the Charity Hospital of Louisiana in New Orleans from 1942 to 1943. He took his Residencies in Scott and White Hospital in Temple in General Sur-

Dr. Preston A. Wade

Dr. H. H. Brindley

gery, and W. C. Campbell Clinic in Memphis, Tennessee, in Orthopaedics. He has taken postgraduate courses at the University of Texas Medical School at Galveston and the University of Tennessee. His present hospital appointment is with Scott and White Memorial Hospital in Temple, in Orthopaedic Surgery.

Graduated From Baylor

Dr. Hinchey was graduated from the Baylor University School of Medicine and took a Fellowship in Orthopaedics at the Mayo Clinic in Rochester, Minnesota. He received his M. S. in Orthopaedic Surgery in 1946 from the University of Minnesota. He is Associate Professor in Orthopaedic Surgery in the University of Texas Graduate School of Medicine in San Antonio, Assistant Professor in Orthopaedic Surgery at the Baylor Graduate School of Medicine and is a consultant at Brooke General Hospital in San Antonio.

Dr. John J. Hinchey

Dr. Hucherson was born in Houston, Texas, took his Internship in Parkland Hospital, Dallas, and his Residency in the University of Louisville Hospitals.

Other officers of the Texas Orthopaedic Association are Dr. Lawrence Griffin of Austin, Vice-President; and Dr. Margaret Watkins, Dallas, Secretary-Treasurer. Dr. B. C. Halley, Jr., of Dallas is Program Chairman for the meeting.

Old Organization

One of the oldest orthopaedic organizations west

Dr. D. C. Hucherson

of the Mississippi River, the Texas Orthopaedic Association had its beginnings thirty years ago and was re-organized as a former organization with a new constitution and by-laws in 1934. Membership in the Texas Orthopaedic Association is limited to men who have passed both sections of the American Board of Orthopaedic Surgery. At present there are 133 members of the Texas Orthopaedic Association in good standing.

The organization meets each year in conjunction with the Texas Medical Association and is devoted to the advancement of Orthopaedic Surgery in the State of Texas. It meets for one day and has a program consisting of formal papers and case presentations.

COMMON COLD

Antihistaminine Chemicals In The Treatment Of The Common Cold:

Report on a Twenty-Seven Month Study

Baughn, W. L., Indust. Mea. & Surg. 19:413, 1950

This report concerns use of antihistaminics in treatment of colds occurring in a large group of industrial workers. It is concluded that these agents provide excellent symptomatic relief.

[The majority of recent reports are far less enthusiastic than the above concerning the value of antihistaminics in treatment of the common cold. Ed.]

Clinical Clippings, December, 1950.

Southwestern New Mexico Medical Society to Meet April 10

The regular meeting of the Southwestern New Mexico Medical Society will be held in Deming, N. M., at 6:30 p. m. April 10 with the Luna-Hidalgo County Medical Society as the host group.

Dr. James D. Bozzell of El Paso will be the principal speaker. He will discuss urological problems in general practice.

Clinical Hypoxia Courses Scheduled in New York

Monthly intensive courses in clinical hypoxia will be held April 5 and 6, May 3 and 4, and June 7 and 8 at the offices of the National Resuscitation Society, 2 East 63rd Street, New York.

These courses have been presented in cooperation with the American Medical Association in New York City and in southern, mid-western and western cities.

More than 1,000 physicians and dentists have received personal instruction in exposing the death zone of the respiratory tract.

Postgraduate Gastroenterology Course Scheduled in Colorado

A three-day postgraduate course on gastroenterology will be presented at the University of Colorado School of Medicine in Denver, May 13-15. The course will offer a broad and intensive review of present day concepts and pertinent recent developments in this field. The faculty will include twenty-eight nationally-known guest physicians who were selected for their authoritative knowledge of their respective subjects.

This exceptional faculty is made possible by the co-sponsorship of the American Gastroenterological Association. The annual meeting of this association will be held at the Broadmoor Hotel in Colorado Springs immediately following the course.

"The Peptic Ulcer Problem" will be the subject of a panel discussion on Tuesday evening at Phipps Auditorium in City Park with six outstanding guest speakers participating. This meeting will be open to all physicians.

In conjunction with the course, the Colorado Society of Internal Medicine will sponsor a dinner meeting at the Albany Hotel on Monday evening. The guest of honor and speaker will be Dr. Hermon Taylor of London, whose subject will be "The Present Status of Medicine in England."

Pan-American Cancer Cytology Congress Scheduled in Miami Beach

The first annual Pan-American Cancer Cytology Congress will hold its sessions April 25-29 in the Eden Roc Hotel in Miami Beach.

Coming Meetings

Southwestern New Mexico Medical Society, April 10, Deming, N. M.

Clinical Hypoxia Courses, April 5 & 6, May 3 & 4, and June 7 & 8, National Resusciation Society, New York.

Border Public Health Association, Apr. 9-12, Hilton Hotel, San Antonio.

Cardiology Review Courses, New York University Postgraduate Medical School, Apr 11 - May 23, and May 6 - 24.

Pan-American Cancer Cytology Congress, April 25-29, Eden Roc Hotel, Miami Beach.

Texas Medical Association, 90th Annual Session, April 27 - May 1, 1957, Dallas. Headquarters, Baker and Adolphus Hotels. Headquarters, Woman's Auxiliary, Statler Hilton Hotel.

Texas Orthopaedic Association, Annual Meeting, April 29, Adolphus Hotel, Dallas.

American Trudeau Society, May 6-9, Kansas City.

Postgraduate Course, Gastroenterology, University of Colorado School of Medicine, Denver, May 13-15.

American Gastroenterological Association Annual Meeting, Broadmoor Hotel, Colorado Springs, May 16.

New Mexico Medical Society, May 15, 16, 17, 1957, in La Fonda Hotel, Santa Fe.

District 8, American College of Obstetrics and Gynecology, Reno, Nevada, May 27 & 28.

American College of Chest Physicians, Annual Meeting, May 29 - June 2, Hotel Commodore, New York.

Postgraduate Course, Management of Chronic Kidney Disease, New York University Postgraduate Medical School, June 24-25.

Postgraduate Course, Management of Hypertension, New York University Postgraduate Medical School, June 26-27.

American Fracture Association, September 30, October 1 and 2, 1957, in El Paso. Dr. W. Compere Basom is in charge of arrangements.

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ORIGINAL ARTICLES

Prevention and Treatment of Blood Transfusion Reactions

(Continued)*

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Pyrogenic Reactions

One might be tempted to include the so-called "pyrogens" among those phenomena which alter the physical properties of the blood, since it appears reasonable to assume they are nothing more than physical agents of molecular size. The infamous pyrogens are probably the most common agents responsible for transfusion reactions.

Yet, paradoxically, the discovery of the exact nature of these agents remains one of the most obscure problems in delineating the etiological factors responsible for transfusion reactions. The name "pyrogen," implying "fever-producing," only adds to the confusion, since most reactions produced by other factors are also characterized by fever. One of the first clear demonstrations of the pyrogenic reaction was made in 1923.[48]

A diagnosis of a febrile or pyrogenic reaction is usually made when the following two criteria are met: (1) a brief (less than four hours) episode of fever and chills of varying degrees of severity developing during or shortly after the completion of a blood transfusion and (2) occurring without serious sequelae and in the absence of evidence of hemolysis, infection, or reaction attributable to other cause.[1,10] This definition, in a sense, makes the term "pyrogenic reaction" a waste-basket for mild types of transfusion reactions.

No Greater Reaction

There is apparently no greater incidence of pyrogenic reactions following the administration of properly preserved blood than of fresh blood.[8] The pyrogenic reaction is reported[1] to be the most common type of blood transfusion reaction, having occurred with an incidence of 2.9 per cent in one study of over 2400 transfusions.[8] It is frequently characterized by mild chills in the absence of fever and change in blood pressure, all symptoms disappearing within 24 hours and death rarely occurring.[1]

Although it is considered to be one of the least serious types of blood transfusion reaction, such a reaction in a debilitated patient may not be harmless.[19] Violent chills, a fever rise of as high as 4°F accompanied by flushing of the skin, nausea, vomiting, and prostration may develop.[1]

The severity of a pyrogenic reaction is proportional to the amount of pyrogenic infused,[1,50] the speed of the infusion, and the susceptibility of the host. It has been noted[8] that the reaction rarely occurs when the recipient of the transfusion is under general anesthesia.

Many Theories

Many theories have been postulated concerning the etiological factors involved, any one or all of which may actually be operative. One of the most popular concepts is that the so-called "pyrogens" responsible for the reaction are chemical substances, breakdown products of bacterial metabolism or altered protein present within the equipment used for blood transfusion.[51,52]

A possibility is that the offending agents are particles of old blood present in improperly cleaned equipment or even foreign protein originating from dead bacteria killed by sterilization.[10]

Still other theories implicate either the recipient of the transfusion, postulating a peculiar hypersensitivity or idiosyncrasy present in the individual, or the particular disease afflicting the recipient, some claims having been made that pyrogenic reactions are almost invariably associated with the infusion of blood into patients having certain diseases.[10] It is claimed[1] that a febrile disease, liver disease, or hypeproteinemia increases patient susceptibility.

Slight Distinction

From the above discussion it seems apparent that the distinction between so-called pyrogenic reactions and anaphylactoid or allergic reactions may be slight indeed. It is not difficult to imagine that all of these reactions are merely gradients of response to the same type of stimulus and actually represent one large family of physical reactions occurring via similar mechanisms.

The pyrogenic reaction may easily be confused with a mild hemolytic or allergic reaction, and, as suggested above, it is quite conceivable that it actually may be a form of the latter. Since it is impossible to differentiate clinically a pyrogenic from an early hemolytic reaction, it is recommended[1] that any trans-

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fusion complicated by the development of the characteristic clinical manifestations of such a reaction be stopped immediately.

The distinction may then be established by appropriate laboratory studies, a positive test for free hemoglobin and bilirubin in the blood indicating the presence of a hemolytic type of reaction.[1] In addition, since it takes 30-45 minutes for a pyrogenic reaction to occur following the initiation of the blood transfusion, it is recommended[10] that a 30-60 minute interval be allowed to elapse before beginning the second of two units of blood which one might intend to infuse simultaneously. In this way the offending unit of blood may be more readily detected, and only one of the two bottles need be discarded, if a reaction develops.

Other Measures

Other general prophylactic measures which may be taken[10] include meticulous care in the cleansing and sterilization of equipment and attention to the purity and quality of blood preservatives. Even more desirable is the utilization of disposable equipment and the reporting of suspicious sets to the manufacturer.

Greater consideration should be given to patients with diseases which predispose toward a hypersensitivity to pyrogens.[10] The most specific prophylactic procedure which may be undertaken is the administration of antipyretics to the patient. Salicylates have been recommended as the best agents to use, one gram of acetylsalicylic acid being given per hour for two hours prior to the intended transfusion and again at the time of the transfusion. This procedure is reported[10] to result in fewer, less severe, or delayed reactions.

Note that the administration of antihistaminics is *not* recommended by some,[10,53] although others[1,54] find it strikingly effective in reducing the incidence of this type of reaction. Clarification of this discrepancy in experimental findings upon which these opinions are based is urgently needed. Once a pyrogenic reaction develops it may be treated symptomatically with aspirin for fever, blankets and hot water bottles for chills, and sedatives if necessary.[1]

Allergic Reactions

The allergic or anaphylactoid type of transfusion reaction is characterized by the development of one or more of the familiar sensitivity responses the sensitized body may be stimulated to make by the introduction of an allergen — namely, a skin rash, pruritus, hives, urticaria or angioneurotic edema (generalized or localized), asthma, serum sickness, and possibly the severe anaphylactoid type of shock.

The latter may be similar to the typical reaction produced by the introduction of horse serum into an individual sensitive to it; that is, loss of sphincter control, asthmatic wheezing and rales, laryngeal edema, and even death.[1,10,32,55,56,57] These allergic states may become manifest during or shortly after the completion of the blood transfusion[10,57] and vary from extremely mild to quite severe reactions.[56]

The incidence of allergic blood transfusion reactions is reported[1] to be second only to that of pyrogenic reactions among untoward responses attributable to blood transfusion, the incidence varying from .5-10 per cent in different reports.[1,10] One group[10] found that only three severe allergic reactions developed in 75,000 transfusions but observed mild reactions with each transfusion in recipients having a wide range of allergies, the over-all incidence being .5 per cent.

It was suggested by these authors that sensitivity to a particular blood fraction may develop in patients receiving numerous transfusions, thus accounting for those recipients who inevitably have reactions with every transfusion. Another observer[32] who estimated that allergic reactions occurred in less than one per cent of all transfusions stated that those patients with allergies to substances in the environment are more likely to develop allergic transfusion reactions.

Allergic types of reaction are reported to have developed in one per cent of 10,000 plasma transfusions[58] and in five out of 400 blood transfusions observed by another group.[59] Still others[8,60] have estimated the incidence of pyrogenic and urticarial reactions to be between 1.8 and 2.7 per cent.

Several Causes

The allergic transfusion reaction may be caused by one or more of the following mechanisms: (1) A specific allergen or foreign protein in the donor's blood may be transferred into a recipient who has a corresponding hypersensitivity to the particular substance.[1,10,61] (2) A specific hypersensitivity or allergy to particular allergens may be passively transferred from an allergic donor to a previously nonallergic recipient.[1,62]

The allergic state thus created in the recipient by the antibodies of the sensitized donor is a temporary one[10] but may last as long as several weeks.[56] The situation is complicated by the fact that some donors are unaware of the existence of their own allergies.[10] (3) Another possibility is that the recipient may be allergic to a specific blood fraction native to the donor's blood but foreign to his.[10,63] In this respect it has been suggested[64] that the allergic reaction may be the result of sensitization of the recipient to blood of a particular donor.

Common Denominator

At present the common denominator of all of these reactions is considered to be an antigen-antibody reaction which results in the liberation of an "allergotoxin" (postulated to be at least in part histamine) which produces the allergic symptoms.[65,67]

Histamine is found in normal living body cells, but an increase in the amount of this substance is known to be associated with allergic states.[1,65] Experiments[6] have been reported which may be taken to substantiate this theory.

Although it is possible for an allergic transfusion reaction to be the result of the transfer of a recently ingested food allergen from the donor into the circulation of a specifically sensitized recipient,[60] this type of reaction is reported to be extremely rare, leading one group to discontinue the routine of instructing prospective donors to fast for four hours prior to giving blood.[10]

The Red Cross does not require the donor to be in a fasting state prior to phlebotomy and actually advises the ingestion of a low protein, low fat, light meal preceding the donation.[1] It might be noted parenthetically here that infusion of blood with an elevated alcohol content, as a consequence of the previous ingestion of alcoholic beverages by an inebriated donor, apparently produces no measurable adverse effects in the recipient.[10]

Blocking Agents

The prevention and treatment of allergic transfusion reactions essentially involves the utilization of antihistaminics as blocking agents[58] and the administration of sympathomimetic drugs in the form of prophylactic and symptomatic therapy. An extremely effective prophylactic procedure is the infusion of washed and resuspended red cells, thus eliminating the transfusion of plasma which is the vehicle carrying the allergens.[10,57] If it is deemed necessary or advisable, the donor may be instructed to fast several hours prior to phlebotomy, or he may be denied food that is on the allergic recipient's restricted food list.[57,68]

Considerable difference of opinion has been expressed concerning the relative value of prophylactic antihistaminics in the prevention of allergic transfusion reactions. Some observers[10] consider the incidence of allergic reactions to be too low to warrant the routine use of prophylactic antihistaminics. However, they advise administration of these agents one hour prior to transfusion in those patients who previously have had allergic transfusion reactions.

Epinephrine Hydrochloride

It has also been found that, if considered advisable, .3 ml of a 1:1000[1] or .50-1.0 cc of a 1:2600[68] solution of epinephrine hydrochloride is quite effective in preventing allergic reactions when added prophylactically to blood. It might be added parenthetically here that the addition of p-aminobenzoic acid systemically to blood is claimed[69] to decrease the number or attenuate the severity of "reactions" of various kinds.

The therapeutic use of antihistaminics following the development of an allergic transfusion reaction is more or less universally accepted[1,10] and the response to this therapy is reported to be excellent.[1]

In addition the administration of adrenalin may definitely be indicated when the more severe allergic reaction occurs. Quick response has been noted[1] following the use of .3 ml of 1:1000 epinephrine hydrochloride, and others[10] reported prompt relief subsequent to adrenalin therapy of all three of the most severe reactions they observed. They also felt that the administration of small doses of intravenous adrenalin is occasionally indicated therapeutically, and this medication should especially be available when the proposed recipient has a history of previous transfusion reactions.

Infectious Disease Agents

Infectious disease agents which may be responsible for blood transfusion reactions include bacteria, viruses, spirochetes, and protozoa.

Bacteria. There are several portals of entry by which offending bacteria may gain access to transfused blood. The most obvious way is for them to be present in the blood stream of the donor.[72] A less obvious but nevertheless omnipresent portal of entry is the deeper layers of the donor's skin which must be pierced during the blood collection phlebotomy. In spite of apparently adequate precautions, including an "aseptic" technique of venipuncture, it is inevitable that bacteria will be introduced into the transfused blood at least occasionally in this manner.[71]

Another unusual portal of entry may be an imperfectly sealed bottle cap or other leaks in the collection or infusion equipment.[72] Probably the most common avenues of contamination, however, are unsterile bottles or transfusion equipment allowed to remain septic by improperly functioning autoclaves.[72] Proof of the existence of this avenue has been further susbstantiated by the actual culture of organisms from washed bottles and tubing prior to their being autoclaved.[73]

Common Contaminators

The most common contaminators of blood designed for transfusion are reported[70] to be small numbers of nonpathogenic diphtheroids, staphylococci, and other Gram-postive organisms, all of which undoubtedly utilize skin or air as portals of entry. Although banked blood is frequently contaminated, most organisms contaminating the stored blood are Gram-postive, few in number, and responsible for the production of minimal reactions.

Most fatal transfusion reactions caused by bacterial contamination, however, are due to relatively nonpathogenic Gram-negative bacilli.[71] The organisms most frequently implicated on smear and culture of offending blood are the non-spore forming enteric rods of the paracolon, coliform, and pseudomonas group.[70-72,74]

Some of the bacteria which have been found responsible for many severe blood transfusion reactions are *Escherichia coli, Pseudomonas aeruginosa, Aerobacter aerogenes, Paracolobactrum aerogenoides,* and

Achromobacter sp.[70,72,73,75] The first two organisms named are responsible for some of the severest reactions occurring in man.[72] The offending coliform organisms, although frequently found in feces, surface water, and soil, may also be found on human skin.[72]

The brucellosis organism, reported[10] to be unaffected by refrigeration, has also been implicated as a blood transfusion contaminant.[8] The toxicity of the infused blood contaminated by these bacteria is not necessarily the result of their inherent pathogenicity *per se,* but rather is a consequence of two characteristics which make them potentially quite harmful.

Capacity To Reproduce

The first is their capacity to reproduce at low temperatures, which enables them to multiply while being stored in the refrigerator, thus making possible the inoculation of large numbers of bacteria in blood which had originally been contaminated by relatively few.[71]

The fact that almost all fatal reactions have occurred following the infusion of blood that has been stored for at least two weeks[76] is consistent with the idea that the offending bacteria multiply while the blood is in storage. This also indicates that there probably is a time lag before the bacteria begin to multiply in dangerously large numbers.[74,76] It is also stated that some of these bacteria are capable of utilizing citrate and actually thrive on citrated stored blood.[72,77]

Second Characteristic

The second characteristic is the phenomenon of the release of endotoxins from these bacteria subsequent to their inoculation.[71] It is stated[72] that they seldom cause actual septicemia. In a group of animal experiments recently reported,[74] it was found that specific antibacterial sera or antibiotics protected mice against the toxicity of blood contaminated with a sufficient number of ordinarily lethal *living* bacteria.

Significantly enough, however, neither of these agents was effective in protecting the animals against the crude endotoxins of the offending bacteria. In addition, only a slightly smaller number of viable than heat-killed bacteria (or their equivalent in endotoxin) was capable of causing death in the mice.

It was inferred, therefore, that the immediate pathogenetic agents were bacterial endotoxins and that if a slightly subcritical or sublethal number of bacteria were inoculated, they could multiply *in vivo* (in the absence of the protective influence of antibiotics or antibacterial sera) to the extent that sufficient endotoxin would then be present to make the inoculation lethal.

The acute reactions and sudden deaths that resulted were attributable more to an "intoxication" by bacterial endotoxins than to an infection, and the efficacy of antibiotics or antibacterial sera in protecting the animals was believed to be a result of their ability to keep the number of offending organisms below the critical level of endotoxin production.

Bacterial Pyrogens

Bacterial pyrogens have been prepared from some of the previously mentioned organisms which have been found pathogenic in blood transfusion reactions, and these pyrogens have been found to produce shock and sudden death in rabbits, at times in the absence of bacteremia and positive blood cultures.[72] These agents, prepared by methods described elsewhere,[78,79] cannot be removed by ordinary bacterial filters and cannot be inactivated by autoclaving.[72]

A reasonable explanation for the less severe reactions produced by pure bacterial pyrogens in comparison to those resulting from inoculation of whole, viable bacteria has already been given. Nevertheless, the injection of purified pyrogens alone is capable of producing severe shock in humans.[80,81]

Transfusion Reactions

The blood transfusion reaction produced by the infusion of blood contaminated with bacteria which are seriously pathogenic in this respect is characterized[10,32,71,72] by the early development of a full feeling in the head, headache, and restlessness. This is usually followed within 10-30 minutes by severe shaking chills and considerable fever.

One hour later, a red flush, resulting from peripheral vasodilatation, may develop and may best be observed in the conjunctivae. By this time nausea, vomiting, diarrhea, and abdominal distress may have ensued. The cardinal feature of a contaminated blood transfusion reaction then supervenes — namely, peripheral vascular collapse.

This is characterized by hypotension, tachycardia, tachypnea, cyanosis, anuria, and uremia. This state of shock may be complicated by a severe septicemia, although the infused bacteria may disappear rapidly from the blood stream and sterile blood cultures may be obtained.

Death usually results via this peripheral vascular collapse, sometimes called "red shock" because of the associated orthostatic hypotension, loss of vasomotor control, and warm, hyperemic skin. It has been noted, however, that although the extremities may be warm initially, they eventually become cold and clammy. Backache and leg pain may also be part of the syndrome.

Death may occur in one to 60 hours, or the patient may recover by lysis over a period of many days. The infusion of as little as 25-40 cc of contaminated blood may result in the recipient's demise.

Endotoxins

The production of transfusion reactions by the endotoxins present in most Gram-negative bacilli is believed to occur as a result of their toxic effect on the peripheral vasculature of the blood recipient.[82-85] These bacterial pyrogens or toxic metabolic products are extremely injurious to blood vessel (including capillary) walls, the primary disturbance in circulation resulting from their action being called bacteremic shock. The latter, incidentally, is characterized by decreased cardiac output and a slightly decreased plasma volume, in addition to hypotension.

Diagnosis. There are three cardinal features of the contaminated blood transfusion reaction that are characteristic enough to constitute guide posts in the differential diagnoses.

The first is the typical reaction, characterized by peripheral vascular collapse, observed clinically in the recipient of such blood.[72]

The second is the demonstration by smear and culture at both room and storage temperatures of the offending bacterial organisms. Since a contaminated blood transfusion reaction may result from the presence of either viable or killed bacteria, it is essential that both smear and culture be performed in an effort to demonstrate the offending organism.[10] It is advised[10] that the recipient's blood as well as donor bottle be studied in this respect. With this in mind, it is recommended[24] that the empty transfusion bottle be kept closed in the laboratory for 24 hours after the infusion is completed, since premature disposal of it would prevent proper investigation of a reaction which had occurred.

Third Feature

The third feature is the demonstration of the presence or absence of hemolysis in the recipient's blood by a determination of the plasma hemoglobin concentration.[86,87] It might be noted parenthetically at this point that the observation of clotted blood in the stored bottle may be a valuable clue indicating the presence of bacterial growth. Many strains of Gram-negative bacteria, especially *Aerobacter aerogenes*, consume citrate, with the result that the blood coagulates.[77]

Prophylaxis. One of the most effective prophylactic measures which must be routinely undertaken is adequate cold storage of the collected blood.[1,70,72] It is recommended[71] that the period of storage be limited to 14 days or less (although the National Institutes of Health permit 21 days of storage).

A second prophylactic procedure is the utilization of strict aseptic technique in the collection, preservation and storage, and administration of blood. As has been suggested, this might be expected to be particularly effective against minor contamination, although gross bacterial contamination can, of course, occur in spite of the most conscientious efforts in this respect.

Proper phlebotomy technique includes as careful sterilization of the donor's skin and collector's hands as is possible.[10] The utilization of disposable collection and administration units cannot be recommended too highly.[72]

If they are not being used, adequate sterilization of all equipment is essential.[10] Reports vary as to the relative safety of the gravity and vacuum types of blood collection sets,[70] some claiming they are equally culpable and others[10] stating that the former is theoretically not as safe from bacterial contamination as the latter.

However, it was warned[10] that unless suitable precautions were taken, the vacuum set would more readily allow bacterial contamination as a consequence of the increased pressure gradient between the internal and external surfaces of the diaphragm lid.

Third Measure

A third prophylactic measure which may be undertaken against contaminated blood transfusion reactions is the prevention of the entrance of air into the transfusion system. Contamination may occur as a result of the entrance of bacteria-laden room air into the transfusion apparatus during the phlebotomy, storage or administration period.

It is extremely dangerous to enter the bottle of stored blood at any time other than immediately prior to infusion of the blood.[10] It was found[70] that contamination was increased by exposure of the blood to room air during the transfusion, the air entering the bottle via the needle which is inserted into the diaphragm lid to facilitate the emptying of blood from the bottle.

However, the natural factors previously mentioned which operate to minimize the dangers of blood transfusion are claimed to have restricted the growth of bacteria thus introduced.[70]

Contamination from unnecessary entrance of air or needles into the bottled blood should be reduced by utilization of the newer collapsible plastic bags in blood collection, storage, and administration.[10] These obviate the need for an air vent, since they do not require displacement of air during their filling or emptying.[10]

No Preservatives

At present there are no chemical preservatives known which may be added prophylactically to blood to successfully prevent contaminated blood transfusion reactions.[88] In animal experiments[74] cortisone was found to be ineffective in suppressing the reaction caused by the infusion of either the bacterial endotoxin or the viable organism.

It goes without saying that the most effective prophylactic measure is an awareness of the dangers inherent in blood transfusion, an awareness which should result in fewer transfusions being prescribed and the smallest inoculum being ordered which will just meet the requirements of the patient.

The smaller the inoculum, the more minimal the hazard.[70] It remains for the future to develop safe and effective methods by which stored blood may be sterilized or bacterial growth suppressed,[10] either by radiation, chemicals, antibiotics, or at present undreamed of techniques.

Treatment. The therapy of contaminated blood transfusion reactions is frequently unsatisfactory because of the very nature of the etiologic agents involved and the pathologic mechanisms by which they act. In the first place the offending organisms are often resistant to most antibiotics. Although antibiotic therapy,[32] including intravenous broad-spectrum antibiotics,[10] has been recommended, there is no assurance that their administration will meet with success.[32]

Reaction May Continue

Secondly, even if the bacteremia is controlled and the offending organism destroyed, the reaction may continue and death may ensue by virtue of the action of the toxic bacterial products on the recipient's circulatory system, since the reaction is not the result of an infection *per se,* but rather an intoxication by products of bacterial metabolism produced during their multiplication in storage.[32] There is no known antidote at present effective against such a poison.[32]

In addition, the circulatory collapse characteristic of the contaminated blood transfusion is not associated with a significant reduction in blood volume,[88] and as a result, therapeutic blood transfusions are not of much benefit in the treatment of the circulatory failure.[32,88]

Obvious Procedure

Aside from the obvious procedure of discontinuing the transfusion when manifestations of a reaction appear, and administering broad spectrum antibiotics, there is little that may specifically be done in the therapy of such a reaction.

Viruses. The incidence of homologous serum jaundice following the intravenous infusion of blood or its derivatives has been the subject of a great deal of consideration. A significant proportion of those who receive such infusions also are the recipients at the same time of numerous needle punctures for other reasons, making the etiology of any ensuing jaundice difficult to ascertain with any certainty.[10,89]

The problem remains a vital but unsolved one, largely because there is no reliable test to detect carriers of the virus[10] and because the offending virus cannot be transmitted to experimental animals. It is possible for an individual to demonstrate serologic but not clinical manifestations of the disease.[90,91]

The disturbing fact remains, however, that the virus may be present in the blood stream of a blood donor in the absence of clinical or laboratory evidence of liver disease, and this carrier may be responsible for the transmission of a fatal disease to the recipient of his blood.[8,71,91] Thus far, there is no known procedure by which the virus may be detected in serum.[10,91]

It has been estimated that one in every 500 cases of fatal hepatitis is the result of blood transfusion. On the other hand, only three deaths from homologous serum hepatitis have been reported following the infusion of 18,000 consecutive transfusions, and another report claims only two or three deaths occurred after 36,000 transfusions.

Hepatitis

Although homologous serum hepatitis occurs as a consequence of the transfusion of whole blood, it develops with an even greater incidence following the administration of pooled plasma.[71,90] This, of course, is because one infected donor can contaminate a large pool of plasma and thus transmit the disease to numerous recipients.

The pooling of the plasma is undertaken to dilute and neutralize isoagglutinins, enabling recipients of any blood group to receive plasma without necessitating the preliminary determination of his group and the administration of compatible plasma.[71]

Pathologically the viruses of homologous serum and viral hepatitis are identical except for the difference in incubation periods of the two diseases they produce, the former being 30-150 days and the latter only 21 days.[90]

Others[10] have described two forms of jaundice which may appear following transfusion. In one the jaundice appears early (a few hours to several weeks after the inoculation) and is associated with fever and hepatitis.

The other is a prolonged afebrile type of jaundice, insidious in onset and developing later (1-6 months after the transfusion), any fever that occurs disappearing rapidly. There is no cross immunity between the two, and the latter type was labeled homologous serum jaundice.

The jaundice that develops as a consequence of viral liver disease must not be confused with that produced by the excessive destruction of red blood cells as a result of either incompatible transfusion reaction or of increased red cell fragility resulting from prolonged or improper storage of blood. And, of course, this hepatocellular type of jaundice must be differentiated from the obstructive type.[90]

Prophylaxis. There is no method absolutely effective in the prevention of homologous serum jaundice, and the administration of blood and its derivatives remains a calculated risk in this respect.[91] The infusion of as little as 2 cc of blood is reported[92] to be sufficient to produce this complication in the recipient.

Five Techniques

Nevertheless, there are five techniques available which will tremendously reduce the hazard of whole blood or plasma-transmitted viral disease, if they are intelligently and faithfully utilized. The first and obvious one is the prescription of blood or plasma as a therapeutic agent as infrequently as possible.

This involves the prevention and treatment of various hypotensive and anemic conditions with specifically indicated agents rather than blood or its derivatives.[93]

For example, the approriate therapy of iron dificiency anemia should be the administration of ferrous gluconate and a specific diet, not whole blood transfusions. In addition, blood substitutes should be administered as often as possible when the amount of blood or plasma estimated to be required for replacement is less than 500 cc.[93]

The second prophylactic procedure that should be undertaken is the careful screening of prospective donors for the history of contact with or presence of jaundice,[10,91] which may have occurred at any time during their lives.[94]

Thirdly, syringes, needles and lancets, the vehicles by which the disease may be transferred from one person to another, should be used for only one donor or patient at a time and heat-sterilized before use.[91] This requires autoclaving them for twenty minutes at 250°F or boiling them in water for thirty minutes.[91]

Fourthly, advantage should be taken of the fact that the virus of homologous serum jaundice tends to die as the plasma containing it ages in liquid form at room temperature. The fact that the storage of plasma for six months or longer at room temperature is a relatively effective method of preventing homologous serum hepatitis has been established[95] and confirmed.[96]

Plasma Pools

Finally, individual units or small pools of plasma should be administered when plasma is indicated and the above mentioned storage conditions cannot be fulfilled. It has been found[10] that refrigeration does not affect the organism and that the plasma-preserving process of freeze-drying also preserves the virus.[71]

This only emphasizes the advisability of utilizing the smaller units of plasma, when the latter has been stored in a frozen state or freeze-dried prior to its use.

Ultraviolet irradiation of whole blood, suggested[97] in 1947 as a means of sterilizing the blood, is impractical at present.[90] Although it is reported[97] to lessen the incidence of homologous serum jaundice, it is not a dependable method of destroying the virus.[71,98]

Various Methods

Various chemical methods[99] have been proposed for the inactivation of the virus of homologous serum jaundice. Nitrogen mustard in a concentration of 500 mg/1 was found[100] to be incapable of inactivating a particular strain of homologous serum virus in whole blood obtained from an individual with the frank disease.

Treatment. Therapy of homologous serum jaundice is essentially supportive and symptomatic. The prescription of a high carbohydrate (400 g), high protein (200 g) diet and bed rest has generally been advised.[101-103]

Spirochetes. Syphilis is readily transmitted by the transfusion of fresh blood. Most cases of transmission occur when the infected donor is in the incubation period or seronegative stage of the disease.[104-106] The secondary lesions of syphilis are usually the first manifestations of the disease to develop in the blood recipient, and they may appear a few weeks to five months after the inoculation.[107] They are more severe than when the disease is acquired in the usual way.[10]

Good Fortune

It is mankind's extreme good fortune, however, that the spirochete dies when stored at refrigerator temperature for 96 hours,[108] a fact that has repeatedly been confirmed.[109] Therefore, in addition to a thorough physical examination of the prospective donor and serology test on his blood for syphilis, adequate prophylaxis against this disease includes the storage of donated blood at refrigerator temperature for at least 96 hours. This simple procedure is remarkably effective in preventing the transmission of syphilis by blood transfusion.

Protozoa. Malaria may be easily transmitted from one infected person to another by transfusion of blood, since the plasmodium survives under all conditions in which red blood cells survive.[10] The interval between the onset of the disease in the donor and the time of his blood donation is of no significance in the transmission of malaria, some people remaining infective up to 25 years following the development of their malaria.[10]

Before a prospective donor who has lived in an endemic area should be accepted as a donor, he should have received malaria suppressive therapy while in the area and should have been asymptomatic for two years thereafter.[10] An infected donor is much more dangerous in nonendemic areas, because the vulnerability of recipients in these areas is much greater.[10]

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Preliminary Report on Experiency With BZ–55 on Ten Diabetics †

By T. E. Hauser, M. D. and E. B. Flanagan, M. D., Carlsbad, N. M.

During the past three months, we have used BZ-55 (Carbutamide)* on ten adult diabetics, all but one having been previously adequately controlled with insulin and diet.

Procedure: Nine patients were hospitalized for institution on BZ-55 therapy. One patient was treated ambulatory for financial reasons. All hospitalized patients had liver and kidney surveys consisting of BSP, TSB, cephalin flocculation, NPN, CBC, and urinanalysis. Insulin was discontinued in the majority one day before admission or the day of admission.

The BZ-55 was started with a daily dose of 2.5 gms. on the first day, 1.5 gms. on the second, and maintained on 0.5 gms. b. i. d. Fasting blood sugars were taken before the onset of therapy with blood sugars taken also at 2:00 P. M. during hospitalization. There was no attempt to change the diet. Following discharge from the hospital, periodic office visits, blood sugars, white blood counts, and urinanalyses have been made.

Case Histories:

Case 1

A 62-year-old motel clerk, duration of diabetes five weeks, 145 lb., followed constantly since July 1953, at which time he had a small stroke with elevated blood pressure, 160/105. On Apresoline 100 mgm. daily to January 1955 when blood pressure was 180/110 and placed on Rauvera q. i. d. Seen periodically in office and felt well, maintained on Rauvera. On 7-19-56, suffered another stroke with paresis of right arm and leg and aphasia.

Routine lab tests all negative. On 8-8-56, became quite irrational. Felt depressed and washed out. Again hospitalized and found to have 3+ glycosuria and fasting blood sugar of 270 mgm. per cent. Was well controlled on 10 units regular insulin t. i. d. On 8-31-56 was placed on BZ-55 without insulin, 2.5 gms. first day and 1.5 gms. daily. No side effects. Fasting blood sugar now 130 mgm. per cent. Patient cheerful and well oriented.

Case 2

A 56-year-old real estate broker, duration of diabetes 36 months, 210 lb. In 1953, treated for diabetes and hypertension. Stayed on treatment for about six months, then discontinued all medication and insulin. First seen on 5-8-56 complaining of anterior chest pain, dizziness, dyspnea. Noticed nocturia 4-5 times nightly and swelling of abdomen for about three months. Temperature - 100, pulse 110, respirations 20, blood pressure 200/130. Lung sounds distant, with rales in both bases, 4+ bilateral pretibial edema.

His decompensation treated with Digitalis, etc. On 7-23-56, insulin was discontinued and BZ-55 started, 2.5 gms. first day, 1.5 gms. the second. On 8-28 blood sugar was 110 mgm. per cent, so BZ-55 reduced to one gm. daily. Since this time, has remained well. Urine sugar free. No side reactions. Blood pressure 140/80 on combination Serpasil and Apresoline q. i. d., Crystodigen 0.2 mgm. daily.

Case 3

A 74-year-old female housewife, hypertensive, duration of diabetes 16 months, 144 lb. Initial blood pressure 200/100. 160/70 after control with Serpasil. Excellent control on 10 units NPH insulin daily. 4+ glycosuria when insulin discontinued for several days in February of 1956. Insulin restarted. Fasting blood sugar was consistently between 130 and 140 mgm. per cent. On one gm. BZ-55 daily and no insulin since 7-2-56, she is under excellent control. Fasting blood sugar is 140 mgm. per cent, and there is no glycosuria.

Case 4

A 47-year-old female housewife and receptionist, hypertensive, duration of diabetes 16 months, 130 lb. Initial B/P 200/100, 170/80 with Apresoline. Excellent control on 10 units of NPH insulin daily. 3+ to 4+ glycosuria when insulin discontinued prior to BZ-55 therapy. Fasting blood sugars 152 to 200 mgm. per cent. On one gm. BZ-55 daily and no insulin since 7-4-56, she is under excellent control. Fasting blood sugar is 131 mgm. per cent, and there is no glycosuria.

Case 5

A 43-year-old male farmer, duration of diabetes five months, 145 lb. Good control on 45 units Lente insulin daily. Fasting blood sugar 120 mgm. per cent. On one gm. BZ-55 daily and no insulin since 7-10-56, he is under excellent control. Fasting blood sugar 120 mgm. per cent, and there is no glycosuria. Weight remains unchanged. Checks urine t. i. d. with testape, and is always negative.

Case 6

A 46-year-old male common laborer, duration of diabetes four months, 210 lb. No insulin therapy before BZ-55. Fasting blood sugar 150 mgm. per cent. Under excellent control on one gm. BZ-55 daily since 6-10-56. Fasting blood sugar 130 mgm. per cent, with no glycosuria.

Case 7

A 41-year-old male common laborer, duration of diabetes seven months, 190 lb. Good control on 40

*BZ-55 (Carbutamide) furnished by Eli Lilly and Co. through its local representative, Bill Sprague, Carlsbad, N. M.

† An article by Dr. Hauser on Orinase will be published in a subsequent issue of SOUTHWESTERN MEDICINE.

units NPH insulin daily. Fasting blood sugar 135 mgm. per cent and no glycosuria. On one gm. BZ-55 daily and no insulin since 7-17-56, is under excellent control, with no glycosuria.

Case 8

A 65-year-old female housewife, duration of diabetes five years, 128 lb. First seen in August, 1953 with severe urinary tract infection and ASHD with decompensation. Always an unstable diabetic because of frequent urinary tract infections due to double kidney and ureter on right. On Crystodigen 0.1 mgm. daily, and 20 units NPH insulin. On 7-26-56, started on BZ-55 three gm. daily and 10 units NPH insulin. Fasting blood sugar 240 mgm. per cent. BZ-55 reduced to two gm. daily and insulin discontinued on 8-17-56. No glycosuria, and blood sugar 160 mgm. per cent. Prognosis as to effectiveness of BZ-55 is guarded.

Case 9

A 56-year-old female housewife, hypertensive, duration of diabetes 28 months, 128 lb., with diabetic retinitis. Hypertension controlled with Inversine from 230/110 to 180/80. Allergic to insulin but finally well controlled on five units Ultra Lente insulin daily. Fasting blood sugars ranged from 78 to 150 mgm. per cent and no glycosuria. On .5 gm. BZ-55 daily and no insulin since 6-18-55, is under excellent control. No glycosuria, and fasting blood sugars range from 72 to 84 mgm. per cent.

Case 10

A 30-year-old male welder, duration of diabetes 12 years, 160 lb. with diabetic neuropathy and diabetic retinitis. Good control on 40 units NPH insulin daily. Fasting blood sugar 245 mgm. per cent. On 1.5 gm. BZ-55 daily since 8-28-56, there is no response except perhaps regulation of glycosuria with smaller doses of insulin. Fasting blood sugars range from 135-330 mgm. per cent.

Comment:

While there is no doubt as to the hypoglycemic effect of BZ-55, the site of action is not known at present. It would appear from the experience of others that it works best in those diabetics who have some functional acinar tissue.

The patients whom we have had on BZ-55 have done well with the exception of Case 10, who has continued to need insulin. He has had diabetes for twelve years, and to date has not responded to BZ-55, but it appears to have helped in regulating his glycosuria with smaller doses of insulin.

Drug rash, agranulocytosis and drug fever reactions have been reported in the literature, the overall side effects in a large series of cases being 6.5 per cent. Recently, there have been reported three deaths due to agranulocytosis.

While nine of our ten patients have had excellent control and have been able to discontinue the use of insulin, the period of follow-up has been relatively short.

Opinions Stated

We feel that BZ-55 may well have a place in treating the older diabetic when it can replace insulin therapy. It is possible to fore-see the addition of BZ-55 to insulin therapy to better control the brittle diabetic in the future.

BZ-55 has worked well, so far, in replacing insulin in nine of the ten patients in this report, the patients having required from five to forty-five units of insulin daily.

We believe one value of this report stems from the fact that these patients were observed in an active clinical practice on a periodic office call basis, rather than many investigative studies that are done on institutionalized patients.

Summary:

1. BZ-55 was given to ten diabetics during the past three months.

2. All but one have been able to discontinue insulin and remain in good control.

3. BZ-55 appears to work best in the elderly diabetic with a short history of diabetes.

4. Continued observation is necessary to detect sign of toxic effects to BZ-55.

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Lilly Suspends Clinical Trial of Carbutamide

Eli Lilly and Company has announced the suspension of the fifteen-month clinical trial of carbutamide, or BZ-55. Carbutamide is a sulfonamide derivative which controls many cases of diabetes when given by mouth.

"We deeply regret that this compound apparently does not meet the rigid requirements for a drug that must be taken throughout life. At the same time, we are grateful that the study of carbutamide was broad enough and thorough enough to uncover its limitations," a Lilly spokesman said.

CPC

Clinical Pathological Conference of The El Paso Medical Society Tumor Clinic

Dr. Maynard Hart, chairman

Presented at the Texas District One Medical Association Meeting at Pecos, February 12, 1957 — Case No. 15,684

Dr. Maynard Hart:

This case presentation of the El Paso County Tumor Clinic will be in the form of a clinical pathological conference. I will not read the history in detail as Dr. Craige prefers to discuss it paragraph by paragraph.

Dr. Branch Craige:

The position of the clinician in a CPC is an honored one, very much like the position of a bull at a bullfight; except here, instead of having only one bull fighter to cope with, the clinician is faced with a group of three pathologists. It seems really like weighing the scales against the poor bull. I shall read the history paragraph by paragraph and discuss the differential diagnosis as we go along.

Present Illness: This 26 year old Mexican male patient was admitted to El Paso General Hospital March 22, 1956. The chief complaint on admission was extreme weakness, associated with dizziness and palpitation. The patient advised that his illness dated back to January, 1956, at which time he experienced increased fatigability, associated with intermittent attacks of fever with occasional chills.

The weakness had steadily progressed and four weeks prior to admission to the hospital, that would be about six weeks after the start of his illness, the patient had periodic episodes of epistaxis and some bleeding from the buccal mucosa. Approximately two weeks prior to admission, the patient developed purpuric spots that started over the arms and spread over the chest and abdomen.

"Little Spiders"

The patient stated that these looked like "little spiders," and that the purpuric areas were associated with a mild rash that was most marked on the volar aspect of the forearms but was also present on the abdomen and was associated with some pruritus.

This lasted several days, but the rash gradually faded. The patient stated that he thought he had a fever at this time, and that he frequently felt chilly.

Also, the patient complained of slight blurring of vision that developed about one week prior to admission and was still bothersome at the time of admission to the hospital.

Summary

In summary, we have a 26 year old male complaining of weakness and palpitation and dizziness and evidence of purpura with fever and chills.

Past History: The past history was essentially negative. A history of the usual childhood diseases was obtained, but there had been no serious illnesses. The patient had lived in Chihuahua most of his life, but had spent two of the past three years in Florida as a fruit picker. The father of the patient was dead of natural causes. It would be interesting to know if these natural causes were blood diseases or not, and the mother, two brothers and one sister were living and well.

Physical Examination: Physical examination at the time of admission to the hospital revealed a young male adult weighing approximately 135 pounds. The temperature on admission was 99.8 degrees. The pulse rate was 80 and uniform, and respirations were 20 per minute.

The blood pressure was normal. There was a marked pallor. No generalized lymphadenopathy could be demonstrated. The spleen was not palpable, and we read further down on the paragraph, "the liver was not palpable" either.

The pupils reacted to light and accommodation. Examination of the fundi revealed scattered small retinal hemorrhages. The buccal mucosa was smooth, and there were no ulcers demonstrated, but very small sub-mucosal hemorrhages on the buccal surface and on the gingiva were noted.

No Neck Rigidity

There was no neck rigidity. The chest revealed no dullness and the breath sounds were normal. It doesn't mention whether or not the sternum was tender.

The heart was of average size and there were no murmurs, which would tend to be against subacute bacterial endocarditis. The abdomen was flat and soft and there were no masses palpable. The external genitalia were grossly normal. The neurological examination was negative.

The physical examination, then, adds very little to what we knew from the history. Thus, we have a

young man, apparently with pallor and anemia, purpura, fever, but no enlargement of the lymph nodes, spleen or the liver.

Laboratory Data: Laboratory data revealed a red blood count of 1,400,000 with 4.4 grams hemoglobin. The white blood count was 7,500 with 66 per cent lymphocytes and 34 per cent granulocytes, and approximately one-half of the granulocytes were juvenile forms or metamyelocytes.

We should remember that in acute leukemia very commonly the first blood count will show a lot of lymphocytes because the first blood count is usually done without thinking about leukemia and the young forms are very often mistakenly counted as lymphocytes.

No nucleated red blood cells were reported. The red blood cells appeared moderately hypochromic. The urine analysis was negative. It seems peculiar, if this young man is bleeding from everywhere else, that there would be no red blood cells in the urine. Specific gravity was 1.026. That would imply, along with the negative urine, pretty good kidneys.

Up to this point, then, we have a disease manifested by purpura with anemia and fever. Could this disease, then, be due to a primary disease or one of the many secondary purpuras? Is it due to intoxication, perhaps exogenous toxin, a poison of some sort? Is it due to an endogenous toxin, such as one might get from uremia? This is unlikely with the normal urine and the high specific gravity. Is it due to some infection? Or, is it due to a primary blood disease, like leukemia? Or, could it be due to something displacing the bone marrow, such as myelophthisic anemia? Well, we'll read on —

Serology Non-Reactive

The serology was non-reactive, and febrile agglutinations, including typhoid, paratyphoid, brucella and Proteus OX 19 were negative. A blood smear for malaria plasmodium was negative. The coagulation time, by capillary tube method, was six minutes and 45 seconds and the bleeding time was eight minutes. The prothrombin-time was 90 per cent of normal.

Apparently he is not bleeding from lack of prothrombin. The red blood cell fragility study was within normal limits. Again, this is not a hemolytic anemia.

The sedimentation rate was 25 mm. in one hour, by which method it doesn't state. The blood sugar was 95 mg. per cent, and the total protein was 7.6 grams with 5.9 grams albumin and 1.7 of globulin.

Urea nitrogen was 16 mg. per cent, which confirms the observation that he is not bleeding from uremia. The direct van den Bergh test was negative and the indirect van den Bergh test was 0.3 mg. per cent. Apparently he is not losing his blood by acute hemolysis or he would have some evidence of weakness.

Stool cultures were negative and no ova or parasites were demonstrated. An L. E. test isn't mentioned, but again in a male with a normal urine, lupus erythematosus is not very likely.

At this time a radiographic examination was done. Would Dr. Boverie like to show the first x-ray?

Dr. Robert Boverie:

There is a little accentuation of the markings there, but I would certainly guess that this is the normal situation to this man. The lung fields are clear. I don't see any nodules, any lesions, at all. I would call it a normal chest.

Dr. Jack Postlewaite:

What about the spleen?

Dr. Boverie:

Well, it doesn't appear to be enlarged nor does the liver appear to be enlarged.

Dr. Rita Don:

A slide of the peripheral blood shows the marked anemia which the patient had. He also had a marked thrombocytopenia. The granulocytes present were occasional myeloblasts, occasional myelocytes and mature polynuclear neutrophiles. In the bone marrow, the picture was essentially the same.

There was an increase in myeloblasts and undifferentiated myelocytes, and we had cells showing Auer bodies.

Dr. Craige:

We have, then, at this point, evidence that this patient had thrombocytopenia which would account for the hemorrhagic tendency; and in the peripheral blood, unusually young cells of the myelocytic series and in the bone marrow, an unusually large percentage of cells of the myelocytic series including a large percentage of young forms.

Course of Illness: Approximately 12 hours after admission the temperature had risen to 100.6 degrees and the patient complained of chilliness, but the patient was not uncomfortable and was able to take a bland diet and rested quietly. A bone marrow aspiration was done and a recheck of the peripheral blood was made.

At this time the peripheral blood revealed the presence of metamyelocytes and myelocytes with a rare myeloblast. The bone marrow also revealed a predominance of cells of the myelocytic stage, and approximately 10 per cent myeloblasts with a granuloerythrocytic ratio of approximately one to one.

Treatment: General supportive measures were carried out, including the transfusion of three units of whole blood. On March 26, four days after admission, the patient had a recurrence of epistaxis and developed purpuric areas over the arms, abdomen and chest.

There was also some bleeding from the buccal mucosa and gingiva. The patient continued to run a

low grade fever, and the temperature fluctuated between 99 and 100.6 degrees. The pulse was stable and rarely exceeded 80 per minute.

A platelet count revealed only 3,000 platelets on March 26, and the reticulocyte count was 1.5 per cent. The count there confirmed Dr. Don's observation from the smear that the platelets were diminished. There is some evidence of production of young red cells in a reticulocyte count of 1.5 per cent.

Repeat peripheral blood studies showed a persistence of relatively immature cells that were interpreted as metamyelocytes or myelocytes. In addition, there now appeared an occasional nucleated red blood cell at the normoblast level. The total white blood count on March 28 had risen to 13,000. But, we note only to 13,000.

The total red blood count was 2,400,000, after two additional units of whole blood. Heparin activity studies and the blood culture were negative.

The negative blood cultures, then, going back to what we mentioned a while ago, gives evidence against bacterial endocarditis.

Doses Increased

On April 1, the patient was started on Meticorten, 5.0 mgs. every four hours for 10 days. This was increased to 10.0 mgs. every four hours for 12 days and then decreased to 5.0 mgs. every four hours again and continued.

General supportive measures were continued, including whole blood transfusions, antibiotic therapy and ascorbic acid and Meticorten. The bleeding from the gums and nose persisted and the temperature fluctuated up to 105 degrees.

Repeat blood cultures were negative. Amidopyrine was given in an attempt to control the fever. A repeat chest film on May 4 revealed bilateral gross infiltrations throughout both lung fields.

Dr. Boverie:

The second x-ray is a portable film, by the way. The lungs are filled with fluffy lesions and the best we can do is give a differential diagnosis. This might be most anything. I would think this may be a pulmonary edema. Any of the granulomatous infections could produce this appearance, metastatic carcinoma or possibly alveolar cell carcinoma may produce such lung fields.

I think pneumonokoniosis might do it. Of course, we know that this is a young man and that a normal film had been made a few weeks before. You wouldn't expect pneumonokoniosis to develop in that short a time.

This is about as far as we can go. My first thought on this film is that it is either a generalized inflammatory process or a pulmonary edema. However, the possibility of metastatic neoplasm or alveolar cell carcinoma cannot be ruled out.

Dr. Craige:

May I ask you? This young man had purpura everywhere else almost. Could purpuric lesions in the lungs give such a picture?

Dr. Boverie:

Well, it possibly could. I have never seen purpuric lesions in the lungs that produced such a picture as this, but I am sure it possibly could if it got that far advanced.

Dr. Craige:

Have you seen myelogenous leukemia infiltrate the lungs to that extent?

Dr. Boverie:

Yes, I have. Not possibly to that extent, but that was one thing I perhaps should have mentioned in the differential diagnosis because the leukemias notoriously can give peculiar changes on the x-ray film.

Dr. Craige:

The clinical history gives us very little more to work with. There is only one more sentence: The patient failed to respond and expired May 6, 45 days after admission.

This is only about four months after the onset of this illness. The diseases that we have been thinking about in differential diagnoses we have mentioned as we have gone through the protocol. I think that with the findings in the bone marrow that Dr. Don has presented, we are limited to one diagnosis, namely, an acute subleukemic myelogenous leukemia.

There are many points in favor of this diagnosis. There was a rather abrupt onset. The age of the patient is relatively young.

There is little in the history that is against such a diagnosis except, as you may have noted, that the liver and spleen and lymph nodes were (the liver and spleen are the important points here) not enlarged, but in acute leukemia occasionally they are not.

Consistent With Diagnosis

The thrombocytopenia, the anemia, the hemorrhagic tendencies and the low grade fever and, ultimately, the high fever are all consistent with such a diagnosis. The negative cultures, the absence of cardiac murmurs when first seen, the normal BUN would help exclude other diagnoses.

The main point about which I remain puzzled is what is this appearance in the lung fields? I should hazard a guess that it is not leukemic infiltration.

It seems to me that if that much infiltration due to myelogenous leukemia were to occur in the lung fields that we should have had by now some enlargement of the liver and spleen or evidence of the leukemic infiltration elsewhere also.

So, my diagnosis would be a subleukemic acute myelogenous leukemia; and I think that the lesions in the lungs are probably edema with or without some hemorrhages.

Dr. Postlewaite:

This disease could be inflammatory or infectious. We could have here nothing more than the blood picture of a myeloid leukemoid response of the blood in which there is the shift of the white cells to the left with low platelets and anemia present.

This leukemoid change of the blood may occur with extreme infections and burn itself out with a person with a poor resistance. The example I think of is tuberculosis. You can certainly get confused in El Paso with tuberculosis.

The second classification that one shouldn't overlook is neoplasia and Dr. Craige has discussed it well, coming to the conclusion that the bone marrow says what the patient died of.

Let's challenge it a minute and suggest some other disease that may not have come up on one puncture of the bone marrow. I think we have made a lot of mistakes clinically because we have accepted the one puncture method of bone marrow study.

For example, Hodgkin's disease at this age is classically the undefined, undiagnosed disease until the termination of the case comes into the pathologist's hands, and then we are embarrassed. We might have offered the patient something.

But there was nothing to suggest Hodgkin's disease physically, and the x-ray might have shown it in the mediastinum and did not. I suppose it's ruled out for that reason.

Another group to be considered is the collagen diseases. The patient might not have had lupus erythematosus but polyarteritis nodosa is classic for the male of this age. The point against it again is the kidney.

I can't see how a terminal disease could occur without the kidney showing this general vascular dysplasia. I asked for the size of the spleen.

One should never diagnose hypersplenism without a palpable spleen.

It should perhaps be kept in mind that there were no nucleated red cells on the original blood smear suggesting exhaustion of the bone marrow. One wonders why nucleated reds were not present until replacement therapy was given.

The appearance of nucleated red cells in any significant proportion of the peripheral blood is a very bad prognostic sign. How the man could have entered the hospital with this low blood count and not have nucleated red cells puzzles me.

It may have been due to some sensitivity problem in which the platelet was the sensitized cell and in which the spleen was hyperactive in its function.

Dr. Frederick Bornstein:

What is your diagnosis?

Dr. Postlewaite:

I don't have one, really. A leukemoid reaction must be considered.

Dr. Craige:

A leukemoid reaction was considered, but we have evidence of primary hematologic disease, namely a striking anemia, immature red blood cells, nucleated red cells in the peripheral blood and a very striking abnormality of the platelets.

Dr. Hart:

I think one factor that might be considered here against leukemoid reaction is the relatively low white count, unless, as Dr. Postlewaite brought out, it is a burned out leukemoid reaction, but ordinarily in a leukemoid reaction you get a pouring out of all elements of the bone marrow, and I would expect to see erythroblasts in the peripheral blood and many nucleated red cells and all stages of granulocytes, not at a fairly definite level like we have here.

There is one little sneaky thing that we did here that we sometimes have to do in CPC's; there were blasts forms in the peripheral blood as Dr. Don presented it.

We didn't mention blasts, we said there were metamyelocytes and I think that Dr. Craige is correct that probably some of the cells that were interpreted as lymphocytes were micrometamyelocytes.

Dr. Bornstein:

Dr. Don, would you please summarize all the findings from the hematological standpoint?

Dr. Don:

He had a severe anemia, he had a severe thrombocytopenia, and in his peripheral blood picture he had myeloblasts, undifferentiated myelocytes and then there was a hiatus with mature polys being present.

The undifferentiated myelocytes were the predominant cells. The picture in the bone marrow was essentially the same. There was a great immaturity in the myeloblasts and the undifferentiated myeloblasts. Again the hiatus was present.

This is referred to as the hiatus leukemicus of Naegeli in which you have an absence of the more mature forms of myelocytes, metamyelocytes, stab forms. They were completely absent from the smear itself, it went from the undifferentiated, extremely immature myelocytes to mature polys.

Dr. Hart:

The fact is that this actually was not a true aplastic anemia inasmuch as we found a 1.5 per cent reticulocyte count and later on nucleated red blood cells began to appear, so I assume that there was no knocking out of the erythropoietic system by a toxin.

Diagnosis of Tumor Clinic: Myeloid leukemia.

Dr. Craige's diagnosis: Acute sub-leukemic myelogenous leukemia.

Pathological diagnosis: Generalized tuberculosis, especially of the thymus, lungs, liver, spleen, lymph nodes and bone marrow.

Pathological Discussion:

Dr. Frederick P. Bornstein:

At autopsy we found the body of a Mexican male looking considerably older than his stated age. He weighed approximately 60 kilograms. There was a mass in the region of the thymus. The mass was of soft consistency and measured about four by four by six cm. The cut surface showed grayish-white tissue which contained numerous small cystic cavities filled with thick greenish pus.

The heart showed superficial petechial hemorrhages. The lungs weighed 2,300 grams. They were extremely firm. The pleurae were studded with numerous bright yellow, soft nodules and a few gray granular nodules.

The cut surface of the lung was dark red. The parenchyma was consolidated and contained the same type of nodules as seen on the surface. The liver showed the same type of nodules on the surface as well as in the parenchyma. The spleen which weighed 450 grams had the most unusual appearance.

Beneath the capsule, numerous yellowish and gray nodules were visible which varied from a few mm. to several cm. in diameter.

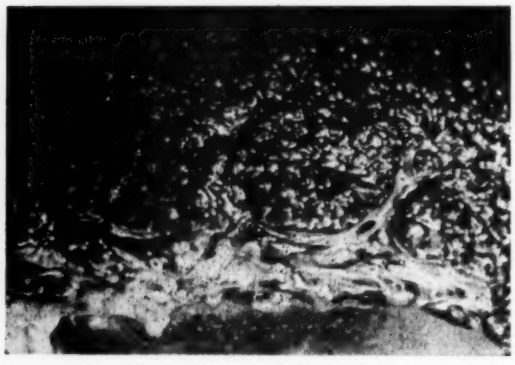

Figure I.

Spleen. Cut surface. Pattern highly suggestive of Hodgkin's disease.

The cut surface of the spleen had lost the normal pattern and instead the surface was densely packed with sharply circumscribed yellowish nodules which gave the spleen an appearance very suggestive of Hodgkin's disease. (Figure I) There was no gross evidence of leukemia.

From the findings at the gross examination I then had the impression that this was not a leukemia but might be a Hodgkin's disease. However, a definite diagnosis had to be deferred for the microscopic examination. The microscopic examination showed a rather peculiar picture, most typical in the spleen. (Figure II)

There were obvious granulomatous foci, the center of which was composed of necrotic material and segmented granulocytes, all surrounded by epitheloid cells.

The picture was somewhat suggestive of a fungus infection, however, special stains revealed the presence of innumerable acid-fast rods typical of tubercle bacilli.

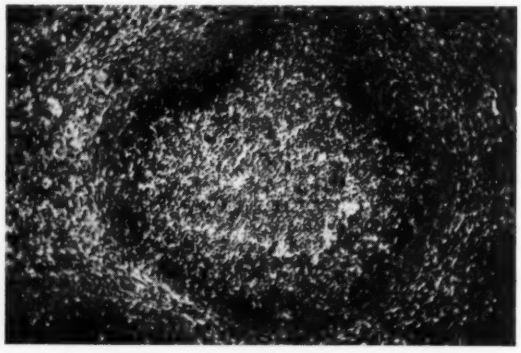

Figure II.

Spleen. Microscopic picture. Purulent granuloma, anergic tuberculosis.

None of the microscopic sections revealed any evidence of leukemia. This picture was fairly uniform in all the organs and acid-fast organisms were demonstrated in all lesions.

Interpretation

Faced with these clinical and pathological findings, what is the interpretation of events? There is very little doubt in my mind that the patient suffered originally from a leukemia and not from a leukemoid reaction. Numerous hematologists to whom we have submitted the slides have agreed with this interpretation.

Reports have been published of cortisone having produced a temporary remission of a leukemia.

We, therefore, have to assume that the cortisone on the one hand produced a remission of the leukemia and on the other hand stimulated a generalized miliary tuberculosis. We all are aware that cortisone has this capacity.

It should be especially emphasized that the gross and histological picture was not typical of tuberculosis, but showed an anergic reaction with a total absence of Langhans' giant cells and a heavy prevalence of segmented granulocytes.

Summary

In summary, we had a patient here with a condition in which cortisone was definitely indicated. Cortisone produced a remission of the original disease and at the same time became responsible for the aggravation and promotion of the final illness.

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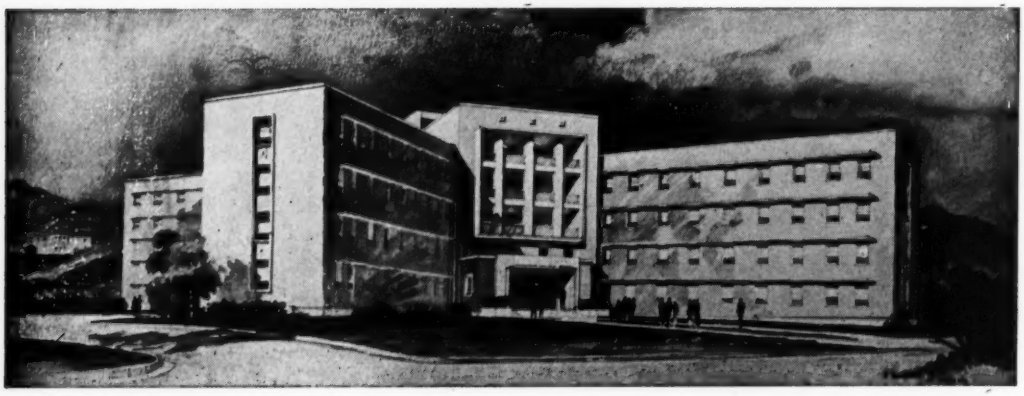

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